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Analysis of the powder behavior and the residence time distribution within a production scale rotary tablet press

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ABSTRACT

This study focuses on the behavior of powder particles in a rotary tablet press with special focus on the feed frame system. To obtain a better knowledge of the continuous manufacturing of tablets, the experimental setup was carried out with a production scale rotary tablet press. The behavior of the powder particles at different flow rates through the tablet press, residual moisture contents, particle sizes, and amounts of tracer was investigated. The residence time distribution was evaluated using the tracer indigo carmine, which was sprayed onto microcrystalline cellulose particle as solution with fluidized bed spray granulator to obtain a tracer blend. The residence time distribution was increased by increasing the amount of tracer blend, and a transition from a plain MCC blend to the tracer blend with regard to continuous manufacturing was shown. Furthermore, it was found that an increase in the flow rates of the powder particles through the tablet press led to a decrease of the residence time distribution (E_t). The variation of the flow rate had no influence on the mechanically applied strain at high throughputs, which was confirmed by a constant number of paddle passes (Npp). At the lowest flow rate, the Npp appears to be higher than the constant Npp values at higher flow rates. The residual moisture content did not shown any significant influence on the residence time distribution. The examination of the effect of different tracer blend particle sizes led to an interesting result: It was shown that the particle size segregation only had a low influence on E_t. However, a comparably higher influence of the particle size segregation on the particle distribution in the produced tablets was demonstrated. Large particles were deposited at the top of the tablet surface whereas small particles were deposited at their bottom.

1. Introduction

The manufacturing of pharmaceutical products becomes more and more cost intensive because of the competitiveness on the global market. Therefore, various pharmaceutical companies, research institutions as well as regulatory agencies are performing research on continuous manufacturing (CM) of pharmaceutical products to extend or replace the traditional batch manufacture (Engisch and Muzzio, 2015; Engisch and Muzzio, 2016; Tian et al., 2017). Thereby, it turned out that CM has the potential to improve pharmaceutical manufacturing (van Snick et al., 2017): A more flexible manufacturing process and an improved robustness of the resulting products are advantages of the CM (Tian et al., 2017). Moreover, the waste which results from the production process is reduced, a smaller footprint is achieved, a faster product development is possible, and an easier scale-up are further benefits of the CM (Lee et al., 2015; Vercruysse et al., 2013). The basic principle of the CM is very simple: The manufacturing steps (e.g. powder feeding of the blender, blending, granulation, compression, and coating) are arranged in series in a single line (Ierapetritou et al., 2016). The raw materials which are added to the system leave the operation unit continuously as end product (Engisch and Muzzio, 2016; Lee et al., 2015).

Other industrial branches have changed their production to CM already years ago. These include the catalysts manufacture (Sudah et al., 2002), mineral processing (Whittles et al., 2005), and also the food processing (Ramaswamy et al., 1995; Torres and Oliveira, 1998). The switch to CM in the pharmaceutical industry proceeds rather slow (Vanarase and Muzzio, 2011). The reasons are the official requirements to ensure the high-quality standards of the pharmaceutical products. The manufacturing of pharmaceutical products is subject to a strict control with a variety of specifications and guidelines that have to be adhered to (Patravale et al., 2016). The quality controls of batch production are performed after each manufacturing step. After these controls, the batch is released for the next manufacturing step. In the case

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of an out-of-specification (OOS) event after the manufacturing step, countermeasures have to be initiated. This type of quality control leads to long dead times between the production steps. The quality controls of the CM are performed during the production process. This makes it possible to initiate countermeasures immediately (Fonteyne et al., 2015; Simonaho et al., 2016). However, a fundamental understanding of the relationship between the process conditions and the behavior of powder material in the continuous manufacturing system is necessary. To obtain such a fundamental understanding of this relationship, the residence time distribution (E_t) may be used (Levenspiel, 1999; Sisay et al., 2017). E_t describes the distribution of the residence time of elements, such as powder particles, inside the operation unit. Thus, differences in the profile shape of E_t may describe the influence of the equipment on the powder behavior (Gao et al., 2011; Vanarase and Muzzio, 2011).

The tableting process is one of the most complex steps during pharmaceutical manufacturing. The tableting process consists of several steps that might influence E_t (Mateo-Ortiz et al., 2014). The different steps are the feeding of the feed frame system by a funnel or pipe (Liss et al., 2004; Prescott and Barnum, 2000), the powder transport through the feed frame system to the dies disc (Ketterhagen, 2015; Mendez et al., 2010), and the filling of the dies (Jackson et al., 2007; Wu and Cocks, 2013). The E_t may be affected by each of these steps.

The residence time of the powder depends on the geometric design of the operation unit (Ketterhagen, 2015) and the operation conditions (Kumar et al., 2015). Mateo-Ortiz et al. simulated the relationship between the residence time distribution and the flow rate of a tracer through a two-chamber filling system by means of a discrete element method (DEM) (Mateo-Ortiz and Méndez, 2015). Mendez et al. also examined the effect of the flow rate of a tracer through a two-chamber filling system but used a die disc replica consisting of a perspex disc for their study. In both cases, the mean residence time decreased whereas the flow rate increased (Mendez et al., 2010). In addition to the flow rate, the particle sizes is of particular importance. Mateo-Ortiz et al. computationally simulated the particle segregation inside a two-chamber filling system and in a die. Results showed that larger particles were observed at the top of the filling system and within the die. Differences between the E_t versus time profiles of various particle sizes fractions were again simulated with DEM (Mateo-Ortiz and Méndez, 2015). These results of the DEM provide a good insight in the effects of the flow rate of tracer through the two-chamber filling system and also of different particle sizes inside the filling system on the particle size segregation.

In the present study, the effect of various amounts of tracer blend, particle size, residual moisture, and different flow rates on the residence time distribution and the powder behavior in a three-chamber feed frame system (Fill-O-Matic) were investigated. The experiments of the study were performed on a production scale rotary tablet press mounted with a three-chamber feed frame system to ensure similar conditions as during industrial tablet manufacturing. The results are intended to provide a more comprehensive process understanding of the influence of the physicochemical powder properties on the E_t versus time profiles, the mean residence time and the mean centered variance. This knowledge is important for the scale-up process and for the development of the feed frame components.

2. Materials and methods

2.1. Materials

2.1.1. Investigated powder blends

The following commonly used types of microcrystalline cellulose were used to approximate the conditions of the industrial tablet manufacturing: Vivapur®102 and Vivapur®200 (JRS Pharma, Germany), which are direct compression ingredients. To improve the flowability of these two filling materials, colloidal silica (Aerosil®200 Pharma, Evonik Industries, Germany) was used as a glidant.

A blue tracer blend was prepared by spray-coloring to determine the powder behavior and the residence time distribution in the Fill-O-Matic (FOM) of a rotary tablet press. The tracer blend consisted of 99.9 [w/w] Vivapur® and 0.1% [w/w] of the blue food colorant indigo carmine (Carl Roth, Germany). During the spray-coloring, indigo carmine was adsorbed to the MCC particles´ surface. For each spray process, 900 g of MCC were spray-colored with 360 ml of 0.25% [w/w] aqueous solution of indigo carmine. A laboratory fluid bed system (Solidlab 1, Bosch, Germany) was used to spray-colour and dry the Vivapur®102 (= tracer blend) to three defined residual moisture contents (wet: 7.37%, medium: 3.88%, dry: 1.39%). To obtain the wet tracer blend, the drying step was stopped directly after the application of the dye solution and for the medium tracer blend the drying step was stopped at a moisture content of 7 g/kg in the Solidlab chamber. For the dry tracer blend, the time period of the drying step was doubled. These residual moisture contents were measured with a moisture analyzer (MA30, Sartorius, Germany).

For the investigation of the particle size segregation, the tracer blend of Vivapur®200 was sieved with metal sieves of different meshes to obtain three tracer blend fractions of different particle sizes: 400–315 µm, 180–125 µm, and < 50 µm. The certificate of analysis specifies the particle size distribution of Vivapur®102 by a d_{50} of 131 µm. Thus, the particles of this MCC type had similar particle sizes as the tracer blend particles from the fraction 180–125 µm.

According to Mateo et al. (Mateo-Ortiz et al., 2014) it is important to ensure identical powder properties of the tracer blend and the MCC blends. However, interactions between the powder particles of the powder blends such as attraction or repulsion, segregation, and lubrication may affect the residence time distribution in the feed frame system.

To confirm the uniformity of both investigated types of MCC, several in-process controls were performed. A laser diffraction unit (Helos, Sympatec, Germany) and a stereomicroscope (SteREO Discovery.V8, Carl Zeiss, Germany) were used to analyze the particle size and its distribution. Moreover, the angle of repose, the bulk density, and the tapped density of the powder were analyzed by an in-process control to show that the powders had the same properties.

2.1.2. Tablet press and feed frame

Tableting experiments were performed with a rotary tablet press (102i, Fette Compacting, Germany) which had been upgraded to a production scale rotary tablet press equipped with 30 pairs of 8 mm diameter punches. This upgrade of the tablet press allowed the generation of results, which were close to production scale. The Fill-O-Matic (FOM) consists of three chambers, positioned at either a high or a low level. The distribution chamber is placed at the high level of the FOM (Fig. 1A) and the dosing and filling chambers at the low level (Fig. 1B). Furthermore, the funnel, which supplies the filling system with powder, was replaced by a feed pipe (Dülle et al., 2018), enabling a uniform powder feed without influencing the powder flow because of the funnel shape (Prescott and Barnum, 2000).

2.2. Methods

2.2.1. Experimental setup

In the present study, four factors characterizing the powder behavior in the FOM were investigated. To provide a more comprehensive knowledge of these factors, the effect of the amounts of tracer blend, the powder flow rates through the FOM, the residual moisture contents, and the powder particle sizes on the residence time distribution was investigated.

To allow an investigation of the influence of the respective factors on the residence time, a consistent basic experimental setup was necessary. Only those factors were changed which were decided to be examined. A 12 mm filling cam with a filling depth of 11.5 mm was